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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,010	09/18/2006	Susan D. Aster	21584P	6490

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EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
09/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,010	ASTER ET AL.	
	Examiner	Art Unit	
	Paul Zarek	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *16-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-22 are currently pending. Claims 16-22 remain withdrawn as being drawn to a nonelected invention. This is the second Office Action on the merits of the claim(s).

RESPONSE TO ARGUMENTS

2. Claims 1-15 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting 11β-HSD-1 comprising administration of an inhibiting amount of a compound of formula I wherein R^2 is methyl, and R^3, R^4, and/or R^5 are:

-H;	C_1-C_6 alkyl;	C_2-C_6 alkenyl;	halogen;
OR^7;	$(CH_2)_nN(R^7)_2$;	cyano;	$-NO_2$;
$-CF_3$;	$-CH_2CF_3$;	$-OCF_3$;	$-OCHCF_2$; and,
$-OCH_2CF_3$,			

does not reasonably provide enablement for a method of inhibiting 11β-HSD-1 comprising administration of another compound not listed above, or treating any condition with the compounds of formula I. Applicant traversed this rejection on the grounds that the instant specification provides sufficient guidance for a skilled artisan to test the claimed compounds, *in vitro* and *in vivo*. Applicant asserts that, since the level of skill in this field is high, it would be considered routine experimentation to determine which compounds would inhibit 11β-hydroxysteroid dehydrogenase-1 (11β-HSD-1) and develop therapeutic protocols to treat conditions responsive to inhibition of 11β-HSD-1. Examiner respectfully disagrees.

3. The instant specification exemplifies 62 compounds of formula I which are encompassed by elected Group II. Applicants have provided *in vitro* and *in vivo* methods by which a skilled artisan could test the compounds of formula I (pg 26 through pg 28). However, Applicants have not disclosed an IC_{50} value for any compound of formula I. Instead, Applicants allege that the compounds of the formula I are "selective inhibitors of the 11β-HSD-1 enzyme" (pg 20, paragraph 5, line 1). As 11β-HSD-1 inhibitors, the compounds of formula I inhibit the conversion of cortisone to cortisol, which is associated with numerous disorders (pg 21, paragraph 1, lines 2-9) and "generally have an inhibition constant IC_{50} of less than about 500 nM, and preferably less than about 100 nM" (pg 23, paragraph 3, lines 1-2). It is unclear which or how many compounds encompassed by formula I actually have an IC_{50} of less than 500 nM, let alone 100 nM. A reasonable alternative reading of this statement, in the context of the entire disclosure, is that compounds utilized for the treatment of a disorder amenable to treatment by inhibiting the 11β-HSD-1 enzyme would have an IC_{50} value of less than about 500 nM, as opposed to all of the compounds having an IC_{50} of less than about 500 nM. In this case, it is unclear just how many compounds of formula I have IC_{50} values of less than about 500 nM.

4. Examiner found no prior art teaching or rendering obvious the claimed compounds of formula I. Thus, Applicants cannot rely on the state of the art to compensate for the deficiencies of the instant specification; specifically, that a significant number of the compounds of formula I actually inhibit 11β-HSD-1. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher* (427 F. 2d 833, 166USPQ 18 (CCPA 1970)) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

5. The instant application is the first disclosure of the compounds of formula I. As such, it bears a heavy burden to enable a skilled artisan to make and use the invention as claimed because the state of the art cannot compensate for any deficiencies within the specification. The instant application provides only a general disclosure regarding the ability of a compound of formula I to inhibit 11β-HSD-1. One of ordinary skill in the art would have no guidance in determining which compound of formula I would both inhibit 11β-HSD-1 and possess pharmacodynamic and pharmacokinetic properties sufficient to exert a therapeutic effect, *in vivo*.

6. As demonstrated by Aster, et al. (Bioorganic & Medicinal Chemistry Letters, 2008, already of record), similar compounds encompassed by formula I, wherein R^1 is phenyl or indolyl, and R^2 is methyl, display varying pharmacodynamic properties. Tables 1-3 disclose the percent inhibition of [^{3}H] cortisone conversion of numerous compounds that are encompassed by the instant claims. Some compounds (i.e. compounds 22, 24, 38, and 39) dramatically inhibit [^{3}H] cortisone conversion (% inhibition of greater than 10%) up to 16 hours following administration of the test compound. However, some demonstrate almost no inhibition, or even negative inhibition either 4 or 16 hours post administration of the test compound (compounds 4, 5, 25, 33, 36, 40, 43, 48, and 49). The experiments disclosed in Aster, et al., demonstrate that subtle changes in formula I can completely abrogate the ability of the specific molecule to inhibit 11β-HSD-1 *in vivo* (compare compounds 4 and 17 in Table 1).

7. Applicants specify a number of diseases and disorders that are potentially amenable to treatment with formula I. The unifying theme behind the listed diseases is the fact that they may comprise an insulin-resistance component, which may be amenable to treatment by 11β-HSD-1 inhibition. If a compound does not inhibit 11β-HSD-1, then it would be unable to treat a

disorder amenable to 11β-HSD-1 inhibition. The instant disclosure provides no guidance for the art worker to predict which compounds of formula I would inhibit 11β-HSD-1, let alone treat a disease amenable to such treatment. Merely indicating an assay by which a skilled artisan can test the ability of the compounds of formula I to inhibit 11β-HSD-1 is not sufficient to enable said artisan to treat a disease. For example, the art worker would be required to determine pharmacokinetic parameters (i.e. bioavailability, clearance), potential adverse drug interactions, contraindications, and formulations to treat a condition amenable to 11β-HSD-1 inhibition. Therefore, the rejection of Claims 1-15 under 35 U.S.C. 112, first paragraph, for not be enabled for the entire scope of the claims is maintained.

Conclusion

8. Claims 1-15 remain rejected.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/San-ming Hui/
Primary Examiner, Art Unit 1617